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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/919,224	07/30/2001	Thomas J. Schall	019934-001710US	5559

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EXAMINER	
BELYAVSKYI, MICHAIL A	
ART UNIT	**PAPER NUMBER**
1644	

DATE MAILED: 08/10/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/919,224	SCHALL ET AL.	
	Examiner	Art Unit	
	Michail A Belyavskyi	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 June 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *21-38 and 44-61* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *21-38 and 44-61* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *06/16/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 06/16/04 has been entered.

Claims 21-38 and 44-61 are pending.

In view of the amendment, filed 06/16/04 the following rejections remain

2. The following is a quotation of the second paragraph of 35 U.S.C. 112.

> *The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.*

3. Claims 26 and 46 stand rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 26 and 46 are indefinite and ambiguous in the recitation of "monitoring the patient to detect amelioration of a symptom associated with the immune disorder". The characteristics and metes and bounds of "a symptom" are unclear , indefinite, not defined by the claim and the specification does not provide a standard for ascertaining what "symptom to monitor".

Applicant's arguments, filed on 06/16/04 have been fully considered, but have not been found convincing.

Applicant asserts that : (i) the term "symptom" is well known in the art; (ii) the specification lists symptoms for 19 different immune diseases.

Contrary to applicants assertion, the issue raised in the previous Office Action was not about the definition of the term "symptom". As was stated previously, applicant only disclosed the symptoms of several specific diseases . However, the terms "immune disorder" and " inflammatory resonse" included diseases that not listed by Applicant and metes and bounds of "a symptom " of said non-listed diseases are unclear , indefinite, not defined by the claim . The specification does not provide a standard for ascertaining what "symptom" associated with said non-listed diseases to monitor after administering rhCMV IL-10 to determine the therapeutic or prophylactic outcome after said administration.

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 21-38 and 44-61 stand rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of inhibiting proliferation of the peripheral blood mononuclear cells , reducing cytokine production of monocytes and reducing surface expression of classical class I and Class II MHC molecules by monocytes *in vitro,* using rhesus CMV IL-10, does not reasonably provide enablement for: 1) a therapeutic or prophylactic method for treating *any* immune disorder, such as the ones recited in claim 24, or allergic response, as recited in claim 34, or asthma, as recited in claim 35 , or leukemia, as recited in claim 38, or *any* chronic inflammatory disease, such as the ones recited in claim 33 or type Th1 immune response to any transplanted graft, for example bone marrow, as recited in claims 36-37, comprising administering a pharmaceutically acceptable dose of rhesus CMV IL-10, as claimed in claims 21-38 and 50-55 or 2) a therapeutic or prophylactic method for treating *any* inflammatory response , such as the ones recited in claim 49, comprising administering a pharmaceutically acceptable dose of rhesus CMV IL-10, as claimed in claims 44-49 and 56-61. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims for the same reasons set forth in the previous Office Action, mailed 03/09/04.

Applicant's arguments, filed 06/16/04 have been fully considered, but have not been found convincing.

Applicant asserts that: (i) the law is clear that in vivo examples are not required to enable treatment claims. *In vitro* examples are sufficient in themselves for one skill in the art to reasonably conclude that administering rhCMV IL-10 could be effective in vivo (ii) two US Patent US Patent 5,770190 and US Patent 5,883,976 have been granted on treatment methods using human IL-10 based, at least in part on in vitro experiments that are similar to those described in the current application ; (iii) in vitro experiments using human IL-10 reasonably correlate with in vivo methods as disclosed in the prior art . The current

application describes a number of in vitro results with rhCMV IL-10 that are related both in terms of experiment protocol and outcome with certain in vitro methods conducted with human IL-10 thus these in vitro results with rhCMV IL-10 would also correlate with in vivo methods; (iv) in the response filed on 1/15/04 Applicant included a chart that list exemplary approaches that could be utilized to identify individuals that could benific from prophylactic treatment

The examiner agrees that *in vivo* examples are not required to enable treatment claims and that symptoms associates with various immune diseases are known in the art. However, as was stated in the previous Office Action, the specification does not adequately teach how to effectively use a therapeutic or prophylactic method for treating an immune disorder , comprising administering a pharmaceutically acceptable dose of rhesus CMV IL-10, as claimed in claims 21-28, 32, 33, 36, 37 and 50-55, or 2) a therapeutic or prophylactic method for treating an inflammatory response , comprising administering a pharmaceutically acceptable dose of rhesus CMV IL-10, as claimed in claims 44-49 and 56-61. Moreover, no animals were used as model system for the therapeutic or prophylactic method for treating an immune disorder or for treating an inflammatory response , comprising administering a pharmaceutically acceptable dose of rhesus CMV IL-10. Since there is no animal model system in the specification to treat an immune disorder , for example GVHD as recited in claim 24, or allergic response, as recited in claim 34, or asthma, as recited in claim 35 , or leukemia, as recited in claim 38, or *any* chronic inflammatory disease, for example rheumatoid arthritis as recited in claim 33 or type Th1 immune response to any transplanted graft, for example bone marrow, as recited in claims 36-37, or an inflammatory response, for example chronic inflammatory disease rheumatoid arthritis, as recited in claim 49, comprising administering a pharmaceutically acceptable dose of rhesus CMV IL-10, it is unpredictable how to correlate test tube results with *in vivo* studies. Thus, although applicant specification describes certain in vitro experiments, there is no correlation on this record between in vitro experiments and a practical utility in currently available form for humans or animals. It is not enough to rely on in vitro studies where, as here, a person having ordinary skill in the art has no basis for perceiving those studies as constituting recognized screening procedures with clear relevance to utility in humans or animals" (emphasis added). Ex parte Maas, 9 USPQ2d 1746.

With regards to the issue that US Patent 5,770190 and US Patent 5,883,976 have been granted on treatment methods using human IL-10 based, at least in part on in vitro experiments.

It is noted that only US Patent '5,770190 teaches the use of human IL-10. There is no recitation of human IL-10 in US Patent 5,883,976. However, it is well settled that whether similar claims have been allowed to others is immaterial. See In re Giolito, 530 F.2d 397, 188 USPQ 645 (CCPA 1976) and Ex parte Balzarini 21 USPQ2d 1892, 1897 (BPAI 1991). Moreover, as stated In re Borkowski, 505 F2d 713,718,184 USPQ29,33 (CCPA 1974), "The Paten Office must have the flexibility to reconsider and correct prior

decisions that may find to have been in error". In a similar context, the court in Fessenden v.Coe, 38 USPQ 516,521 (CADC 1938) stated that '[t]wo wrongs cannot make a right."

It is the examiner position that the *in vitro* examples provided by the Applicant do not correlate with *in vivo* studies. There must be a rigorous correlation of pharmacological activity between the disclosed in vitro utility and an in vivo utility to establish practical utility. Since the method to treat an immune disorder , for example GVHD as recited in claim 24, or allergic response, as recited in claim 34, or asthma, as recited in claim 35 , or leukemia, as recited in claim 38, or *any* chronic inflammatory disease, for example rheumatoid arthritis as recited in claim 33 or type Th1 immune response to any transplanted graft, for example bone marrow, as recited in claims 36-37, or an inflammatory response, for example chronic inflammatory disease rheumatoid arthritis, as recited in claim 49, comprising administering a pharmaceutically acceptable dose of rhesus CMV IL-10, can be species- and model-dependent, it is not clear that reliance on the test tube studies accurately reflects the relative human efficacy of the claimed therapeutic strategy. The specification does not adequately teach how to effectively treat an immune disorder or an inflammatory response comprising administering a pharmaceutically acceptable dose of rhesus CMV IL-10. The specification does not teach how to extrapolate data obtained from *in vitro* studies to the development of effective *in vivo* mammalian including human therapeutic treatment, commensurate in scope with the claimed invention. Moreover, it is noted that the prior art references provided by Applicant supports the Examiner position. For example, Lindsay et al teaches that in vitro data using human IL-10 and therapeutic efficacy of IL-10 in patient is not clear cut (see, page 1713 in particular), Steinhart teaches that there was no increase in the proportion of patient achieving clinical reemission at the end of treatment with human Il-10. Steinhart further teaches that as a result the redundancy in the immune response likely allows other pathways that are not blocked or modified by IL-10 to adjust their activity. For IL-10 to produce a clinically meaningful benefit and to determine the efficacy of human IL-10 in patient further studies have to be done (see page 801 in particular). Similarly, Opal et al, teach that ultimate clinical utility of IL-10 in infectious diseases and other human disease states remains to be determined through carefully performed clinical trails. It is incumbent upoun the infectious disease physician to be cognizant of the anticipated risks of IL-10 administration in humans. It appear that IL-10 is a double-edged sword in the presence of systemic infection (see pages 1502 and 1504 in particular) Lockridge et al. teach that CMV IL-10 is a multifunctional cytokines that has various effects on inflammation and cytokine production and that further studies will be necessary to determine its role in the immunopathogenesis. (see entire document, page 278 in particular). Additionally, Bals R., et al., (Infection and Immunity, 1999, v.67, pages 6084-6089) teach that functional studies have been restricted primarily to *in vitro* experiments with purified peptides and do not necessarily reflect the complexity of *in vivo* interaction, such as synergism and antagonism between individual substances (

see overlapping pages 6087-6088 in particular). Mountain reviews in Trends Biotechnol (18:119-128, 2000) that while much progress has been made in the field of gene therapy, developing effective gene therapies is much more demanding than originally anticipated (e.g., pg 120, middle); and that most of the difficulty lies with the development of effective vectors since the vectors in use all have both advantages and disadvantages (e.g., Table 4). Additionally, an effective protocol to treat an immune disorder or an inflammatory response comprising administering a pharmaceutically acceptable dose of rhesus CMV IL-10, is subject to a number of factors which enter the picture beyond simply the administration of the therapeutic composition in an acceptable formulation. Demonstrating that contacting PBMCs with rhesus CMV IL-10 inhibits PBMC proliferation and cytokine production and reduces monocytes surface expression of classical class I and class II MHC cannot alone support the predictability of a pharmaceutically acceptable dose of rhesus CMV IL-10 for a therapeutic or prophylactic method for treating an immune disorder or an inflammatory response through administration of the appropriate formulation. Van Noort et al. (International Review of Cytology, 1998) indicate factors that effect autoimmune disease such as genetic, environmental and hormonal (Page 176, Paragraph 3). The ability of a host to suppress an immune disorder or an inflammatory response will vary depending upon factors such as the condition of the host and burden of disease. Thus, there is no evidence of record that experimental animal models have been developed in this area which would be predictive of human efficacy." Ex parte Balzarini, 21 USPQ2d 1892.

The specification does not provide sufficient teaching as to how it can be assessed that treatment of an immune disorder , for example GVHD as recited in claim 24, or allergic response, as recited in claim 34, or asthma, as recited in claim 35 , or leukemia, as recited in claim 38, or *any* chronic inflammatory disease, for example rheumatoid arthritis as recited in claim 33 or type Th1 immune response to any transplanted graft, for example bone marrow, as recited in claims 36-37, or an inflammatory response, for example chronic inflammatory disease rheumatoid arthritis, as recited in claim 49, was achieved after the administering of a pharmaceutically acceptable dose of rhesus CMV IL-10.

It is also noted that the issue raised in the previous Office Action, mailed on 03/09/04 was not about identifying individuals that could benefit from prophylactic treatment. As was stated in the Previous Office Action the burden of enabling prophylactic an immune disorder or an inflammatory response (i.e. the need for additional testing) would be greater than that of enabling a treatment due to the need to screen those humans susceptible to such diseases and the difficulty of proof that the administration of the drug was the agent that acted to prevent the condition. Further, the specification does not provide guidance as to how one skilled in the art would go about screening those patients susceptible to an immune disorder or an inflammatory response within the scope of the presently claimed invention. Nor is guidance provided as to a specific protocol to be utilized in order to prove the efficacy of the presently claimed compounds in preventing these disease states. Accordingly, undue experimentation is necessary to determine

screening and testing protocols to demonstrate the efficacy of the presently claimed invention.

Thus, Applicant has not provided sufficient guidance to enable one skill in the art to use claimed: 1) a therapeutic or prophylactic method for treating *any* immune disorder, such as the ones recited in claim 24, or allergic response, as recited in claim 34, or asthma, as recited in claim 35 , or leukemia, as recited in claim 38, or *any* chronic inflammatory disease, such as the ones recited in claim 33 or type Th1 immune response to any transplanted graft, for example bone marrow, as recited in claims 36-37, comprising administering a pharmaceutically acceptable dose of rhesus CMV IL-10, as claimed in claims 21-38 and 50-55 or 2) a therapeutic or prophylactic method for treating *any* inflammatory response , such as the ones recited in claim 49, comprising administering a pharmaceutically acceptable dose of rhesus CMV IL-10, as claimed in claims 44-49 and 56-61 in manner reasonably correlated with the scope of the claims. The scope of the claims must bear a reasonable correlation with the scope of enablement. *In re Fisher*, 166 USPQ 18(CCPA 1970) indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute.
In view of the quantity of experimentation necessary, the unpredictability of the art, the lack of sufficient guidance in the specification, the limited working examples, and the limited amount of direction provided given the breadth of the claims, it would take undue trials and errors to practice the claimed invention.

6. No claim is allowed.

7. This is a RCE of applicant's earlier Application No. 09/919224 . All claims are drawn to the same invention claimed in the earlier application and could have been finally rejected on the grounds and art of record in the next Office action if they had been entered in the earlier application. Accordingly, **THIS ACTION IS MADE FINAL** even though it is a first action in this case. See MPEP § 706.07(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no, however, event will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michail Belyavskyi whose telephone number is 571/272-0840. The examiner can normally be reached Monday through Friday from 9:00 AM to 5:30 PM. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on 571/272-0841.

The fax number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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